The Oncologist®

Gastrointestinal Cancer

Immune-Related Adverse Events and Immune Checkpoint Inhibitor Efficacy in Patients with Gastrointestinal Cancer with Food and Drug Administration-Approved Indications for Immunotherapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immune-related adverse events • Immune checkpoint inhibitor efficacy • Clinical biomarker • Gastrointestinal cancer

Abstract

Introduction. Immune-related adverse event (IRAE) onset may represent a clinical biomarker for anti-programmed cell death protein 1 (PD-1) antibody response based on emerging evidence from patients with various advanced malignancies. This phenomenon has not been previously reported in a multidisease cohort of patients with gastrointestinal (GI) cancer with Food and Drug Administration (FDA)-approved indications to receive immune checkpoint inhibitor therapy.

Materials and Methods. The study was a multicenter retrospective cohort analysis of 76 patients with GI cancer who had received anti-PD-1 antibodies for FDA-approved indications. The primary and secondary outcomes of the study were progression-free survival (PFS) and overall survival (OS) in patients based upon IRAE presence, respectively. PFS and OS were estimated by the Kaplan-Meier method; a Cox proportional-hazards model adjusted for IRAE onset, patient age, and enrolling institution was used to analyze outcomes.

Results. Median PFS and OS were prolonged in patients who experienced IRAEs compared with those who did not experience them (PFS: not reached [NR] vs. 3.9 months [hazard ratio (HR) 0.13, 95% confidence interval (CI) 0.05–0.3, $p < .001$]; OS: NR vs. 7.4 months [HR 0.11, 95% CI 0.03–0.36, $p < .001$]). Among patients who experienced IRAEs, there were no significant differences in PFS and OS by either initial IRAE severity, management, or time to onset.

Conclusion. Patients with gastrointestinal cancer who experienced IRAEs while on anti-PD-1 antibodies demonstrated significant improvements in PFS and OS compared with their counterparts who did not develop IRAEs. Although these findings add to results from studies in other tumor types, larger prospective studies are needed prior to clinical adoption of IRAE onset as a biomarker for immune checkpoint inhibitor response. ***The Oncologist*** 2020;25:669–679

Implications for Practice: Predictive clinical biomarkers for immune checkpoint inhibitor response have been understudied in the field of immuno-oncology. Immune-related adverse event onset appears to be one such biomarker. Across tumor types, immune-related adverse event onset has been associated with response to anti-programmed cell death protein 1 (PD-1) antibodies. The results of this study demonstrate this for the first time in patients with gastrointestinal cancer receiving anti-PD-1 antibodies. Before immune-related adverse event onset can be adopted clinically as a predictive biomarker for immune checkpoint inhibitor response, however, larger prospective studies are needed to better understand the nuances between immune-related adverse event characteristics (severity, site, management, timing of onset) and immune checkpoint inhibitor effectiveness.

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Introduction

Despite the transformative therapeutic potential of immune checkpoint inhibitors (ICIs), relatively few patients with gastrointestinal (GI) cancer are eligible to receive the agents [1–5]. Some of the Food and Drug Administration (FDA)-approved indications for ICIs in patients with GI cancer include pembrolizumab for later-line microsatellite instability–high (MSI-H) tumors, nivolumab or nivolumab plus ipilimumab for refractory MSI-H colorectal cancer (CRC), nivolumab for second-line or sorafenib-ineligible hepatocellular carcinoma (HCC), and pembrolizumab for programmed death-ligand 1 (PD-L1)–positive (combined positive score [CPS] ≥1) third-line gastric (GA)/gastroesophageal (GEJ) adenocarcinoma [6–10]. Even in patients who are eligible, optimal response rates (RRs) with the agents range from 20% to 50%, leaving a significant proportion of patients who do not respond. This dilemma has led to an ongoing search for biomarkers that can better select patients who might respond to ICIs and better identify patients who are responding to the agents. The search thus far has primarily focused on tumor signatures such as MSI-H, homologous recombination defects, tumor mutational burden (TMB), and PD-L1 expression; clinical biomarkers have been less rigorously studied [5, 11, 12].

Immune-related adverse events (IRAEs) may represent one such biomarker given emerging data in non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, GA/GEJ and others suggesting that patients who experience IRAEs while on therapy with anti-programmed cell death protein 1 (PD-1) or anti-PD-L1 antibodies have significantly improved outcomes (progression-free survival [PFS], overall survival [OS], RR) compared with those who do not [13–19]. The focus of our analysis was to assess this phenomenon in patients with GI cancer with FDA-approved indications to receive ICI therapy.

Materials and Methods

Patients

We performed a multicenter retrospective cohort analysis of 76 patients with metastatic or unresectable GI cancer receiving anti-PD-1 antibodies for FDA-approved indications (later-line MSI-H tumors, second-line or sorafenib-ineligible HCC, third-line PD-L1–positive [CPS ≥1] GA/GEJ adenocarcinoma), at Vanderbilt Ingram Cancer Center (VICC), Winship Cancer Institute of Emory (WCE), and Stanford Cancer Institute (SCI). We chose to include only patients receiving ICIs for FDA-approved indications in order to maximize our ability to detect a differential efficacy signal in patients by IRAE presence, if one truly existed. Patients who were analyzed were treated between July 10, 2014, and December 20, 2018, and received at least one dose of anti-PD-1 antibody, as monotherapy or in combination with ipilimumab.

Data

Institutional research board approval was obtained from each participating institution prior to data collection. Data was collected from chart abstraction from the electronic medical record systems Epic and Cerner PowerChart by three medical doctor investigators. The data collection instrument was created through a REDCap database at VICC before being distributed to participating investigators at WCE and SCI. The instrument, along with the raw data, is included in supplemental online Appendix 1. IRAEs were documented for patients if they were organ specific (involving dermatologic, musculoskeletal, endocrine, gastrointestinal, renal, cardiac, or other systems) and were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by a single investigator at each institution. Primary tumor type was categorized by the predominant tumor types represented in the analysis (MSI-H CRC, HCC, and other tumors). The other tumor category included patients with PD-L1–positive GA/GEJ and MSI-H duodenal, bile duct, neuroendocrine, and pancreatic tumors.

Several terms were defined at the time of study design in order to ensure data collection consistency. Time on immunotherapy was defined as time between first documented immunotherapy dose to last documented immunotherapy dose. Date of progression was the date on which the patient progressed on restaging scans (computed tomography, positron emission tomography–computed tomography, or magnetic resonance imaging). Response endpoints (partial response, complete response, stable disease, progressive disease) were assessed by RECIST 1.1 and were determined by institutional radiologists from each of the participating institutions. In instances where patients never developed disease progression prior to death, date of death was used as the date of progression. Patients who did not experience disease progression or death were censored by the date of their last follow-up visit in any clinical setting.

Statistical Analysis

The primary objective of the analysis was to compare PFS between patients who did and did not experience IRAEs. The secondary objective of the analysis was to compare OS between patients based on the presence or absence of IRAEs. Prespecified subgroup analyses included comparing PFS and OS in the cohort of patients who experienced IRAEs by initial IRAE severity (grade [G]3/G4 vs. G1/G2), time to onset (TTO; <6 weeks vs. ≥6 weeks), and management (steroidal vs. nonsteroidal). Exploratory subgroup analyses included comparing PFS and OS in patients who experienced IRAEs, by site of initial IRAE and total IRAE number (>1 vs. 1).

Sample size estimation was completed using the log-rank test; details are included in supplemental online Appendix 2. With the proposed sample size of 66 patients (33 with IRAEs and 33 without IRAEs), there was at least 80% power to detect a hazard ratio of 0.5 with two-sided type I error of 0.05. This calculation was based on the assumption that median PFS for patients without IRAEs is 3.5 months and follow-up time is 24 months [13–15]. The Kaplan-Meier method was used to estimate PFS and OS. The log-rank test was employed for examining PFS and OS differences between study groups. The elastic net regularization path was used for variable selection in the Cox proportional-hazards model; each examined variable was an independent prognostic factor associated with the outcome. The variables that were examined were IRAE

onset, receipt of anti-PD-1 antibodies on a clinical trial, primary tumor type, patient age at ICI start, and enrolling institution. The final Cox proportional-hazards model included IRAE onset, patient age at ICI start, and enrolling institution; specifics of this model are described in supplemental online Appendix 3. Time on immunotherapy was not included in the model as a variable given existing data that IRAE incidence does not increase in patients based on longer ICI exposure [16, 20, 21]. A time-dependent covariate analysis for IRAE onset, however, was performed and is included in supplemental online Appendix 5. Statistical analyses were conducted using R package (version 3.5.3). The results were considered statistically significant when two-tailed *p* values were <.05.

Results

Outcomes in 76 patients with GI cancer, treated with anti-PD-1 antibodies between July 2014 and December 2018, were analyzed. Among these patients, 38 (50%) were treated at VICC, 29 (38%) at SCI, and 11 (12%) at WCE. The median patient age was 63, with 52 (68%) men and 24 (32%) women. The predominant primary tumor types represented in the analysis were HCC (42%), CRC (38%), and GA/GEJ (12%). MSI-H status was known and positive in 35 (46%) patients; the predominant subtype of MSI-H tumors was CRC (82%), whereas rarer subsets included pancreatic (9%), duodenal (3%), biliary (3%), and neuroendocrine carcinoma (3%). TMB was available for only 17 (22%) patients, whereas only the 8 (12%) patients with gastric/GEJ cancer possessed tumors that were tested and positive for PD-L1 expression. Patients with HCC, CRC, and other tumors received one, two, and two median lines of therapy prior to anti-PD-1 therapy, respectively. A total of 76 (100%) patients were treated with anti-PD-1 antibody monotherapy, with 43 (57%) and 33 (43%) receiving nivolumab and pembrolizumab, respectively. Patients remained on anti-PD-1 antibody therapy for a median of 6.9 months. A detailed summary of patient characteristics is given in Table 1.

IRAEs developed in 33 (43%) patients with a median time to onset of 4.4 months. Of the 47 total IRAEs experienced by patients, 34 (72%) were G1/G2, whereas 13 (28%) were G3/G4. The most common sites of IRAE involvement were musculoskeletal (28%), dermatologic (26%), and endocrine (21%) systems, whereas gastrointestinal (11%), cardiac (4%), and renal (2%) systems were rarely involved. Within gastrointestinal IRAEs, no cases of diarrhea or colitis were documented; however, 23% of patients had baseline G1 diarrhea prior to starting ICI therapy. IRAEs were managed supportively in most patients (62%), whereas steroids (26%) and drug cessation (12%) were utilized less frequently. Details of all individual IRAEs and how they were managed are listed in Table 2. Patients with MSI-H tumors had a greater likelihood of developing IRAEs compared with patients whose tumor MSI status was unknown ($p = .003$ by Fisher's exact test). No significant difference in initial IRAE grades was observed between patients with MSI-H tumors and patients with MSI-unknown tumors ($p = .214$ by Fisher's exact test).

Median PFS and OS were prolonged in patients who experienced IRAEs compared with those who did not experience them, across the entire cohort (PFS: not reached [NR] vs. 3.9 months [hazard ratio (HR) 0.13, 95% confidence interval (CI) 0.05–9.3; $p < .001$]; OS: NR vs. 7.4 months [HR 0.11, 95% CI 0.03–0.36, $p < .001$]; Fig. 1A and B). This association was maintained when patients were separated by primary tumor type and by gender. In patients with CRC, median PFS (NR vs. 4.8 months [HR 0.05, 95% CI 0.01–0.41, $p < .001$]) and OS (NR vs. 15.9 months [HR 0, 95% CI 0–∞, $p = .001$]) were longer in patients who experienced IRAEs compared with those who did not (Fig. 2A and B). In patients with HCC, median PFS (NR vs. 3.5 months [HR 0.3, 95% CI 0.09–1.03, $p = .042$]) and OS (NR vs. 6.5 months

Table 1. Baseline characteristics of the study population

Patient characteristics	*n* (%)
Gender	
Male	52 (68)
Female	24 (32)
Received ICI on clinical trial	
No	62 (82)
Yes	14 (18)
Primary tumor site	
Hepatocellular	32 (42)
Colorectal	29 (38)
Other	15 (20)
Gastric or GEJ	9 (12)
Pancreas	3 (4)
Bile duct	1 (1.3)
Neuroendocrine carcinoma	1 (1.3)
Duodenal	1 (1.3)
MSI-H status	
Unknown	41 (54)
Known	35 (46)
TMB status	
Unknown	59 (78)
Known	17 (22)
Disease stage	
Metastatic	76 (100)
Institution	
VICC	38 (50)
SCI	29 (38)
WCE	9 (12)
Checkpoint inhibitor received	
Monotherapy	76 (100)
Nivolumab	43 (57)
Pembrolizumab	33 (43)
IRAE	
No	43 (57)
Yes	33 (43)
Single	22 (29)
Multiple	11 (14)

Abbreviations: GEJ, gastroesophageal junction; ICI, immune checkpoint inhibitor; IRAE, immune-related adverse event; MSI-H, microsatellite instability–high; SCI, Stanford Cancer Institute; TMB, tumor mutational burden; VICC, Vanderbilt Ingram Cancer Center; WCE, Winship Cancer Institute of Emory.

Table 2. IRAE characteristics and management

Site of IRAE	IRAE grades			Management		
	Grade 1/2 (*n* = 34)	Grade 3/4 (*n* = 13)	All grades (*n* = 47)	Support-ive care[a] (*n* = 29)	Steroids (*n* = 12)	Drug cessation (*n* = 6)
MSK (*n* = 13)						
Myositis		1	1			1
Arthralgias	11	1	12	7	3	2
Endocrine (*n* = 10)						
Hypothyroidism	4		4	4		
Thyroiditis	1		1	1		
T1DM	1	3	4	1	3	
Adrenal insufficiency		1	1	1		
Dermatologic (*n* = 12)						
Rash	5	2	7	4	3	
Pruritus	3		3	3		
Lichen planus	1		1	1		
Lichenoid keratosis	1		1	1		
GI[b] (*n* = 5)						
Hepatitis	1	3	4	1	1	2
Mucositis	1		1	1		
Renal (*n* = 1)						
Nephritis	1		1			1
Cardiac (*n* = 2)						
Myocarditis		2[c]	2		2	
Other (*n* = 4)						
Fever	1		1	1		
Conjunctivitis	1		1	1		
Sicca	2		2	2		

[a]Supportive care included topical steroids, thyroid hormone and cortisol replacement, and nonsteroidal agents.
[b]In the patients in the analysis, 23% experienced baseline grade 1 diarrhea. No flares of this were observed during checkpoint inhibitor treatment, and thus diarrhea was not counted as an IRAE in the analysis.
[c]One of the two patients had a grade 5 event that resulted in her death, 8 months after she had stopped pembrolizumab.
Abbreviations: GI, gastrointestinal; IRAE, immune-related adverse event; MSK, musculoskeletal; T1DM, type 1 diabetes mellitus.

[HR 0.17, 95% CI 0.02–1.32, p = .055]) were prolonged in patients with IRAEs compared with those without; OS differences in this cohort did not meet statistical significance (Fig. 2C and D). In patients with other primary tumors, median PFS (NR vs. 4.9 months [HR 0.2, 95% CI 0.04–1.08, p = .039]) and OS (NR vs. 5.1 months [HR 0.2, 95% CI 0.04–1.16, p = .05]) were prolonged in patients who experienced IRAEs compared with those who did not (Fig. 2E and F). In men, median PFS (NR vs. 3.5 months [HR 0.17, 95% CI 0.07–0.46, p < .001]) and OS (NR vs. 7.4 months [HR 0.17, 95% CI 0.05–0.61, p = .002]) were longer in patients who experienced IRAEs compared with those who did not (supplemental online Fig. 1A and B and Appendix 4). In women, median PFS (NR vs. 3.9 months [HR 0.05, 95% CI 0.01–0.44, p < .001]) and OS (NR vs. 5.1 months [HR 0, 95% CI 0–∞, p = .003]) were also prolonged in patients who experienced IRAEs compared with those who did not (supplemental online Fig. 1C and D and Appendix 4).

Among patients who experienced IRAEs, there were no significant differences in median PFS and OS between those who experienced G3/G4 adverse events versus those with G1/G2 adverse events (PFS: NR vs. NR [HR 0, 95% CI 0–∞, p = .075]; OS: NR vs. NR [HR 0, 95% CI 0–∞, p = .195]; Fig. 3A and B), those who required steroidal versus nonsteroidal management (PFS: NR vs. NR [HR 1.2, 95% CI 0.27–5.37, p = .811]; OS: NR vs. NR [HR 0.72, 95% CI 0.07–7.01, p = .76]; Fig. 3C and D) and those who experienced IRAE TTO <6 weeks versus ≥6 weeks after starting ICIs (PFS: NR vs. NR [HR 1.07, 95% CI 0.13–8.97, p = .949); OS: NR vs. NR (HR ∞, 95% CI 0–∞, p = .389]; Fig. 3E and F). There were no significant differences in median PFS and OS among patients who experienced IRAEs based on total IRAE number (>1 vs. 1) or IRAE site (supplemental online Figs. 3 and 4 and Appendix 4).

Discussion

We found significant improvements in PFS and OS between patients with GI cancer receiving ICIs for FDA-approved indications who experienced IRAEs while on treatment compared with patients who did not experience IRAEs. This difference was maintained in patients when separated by

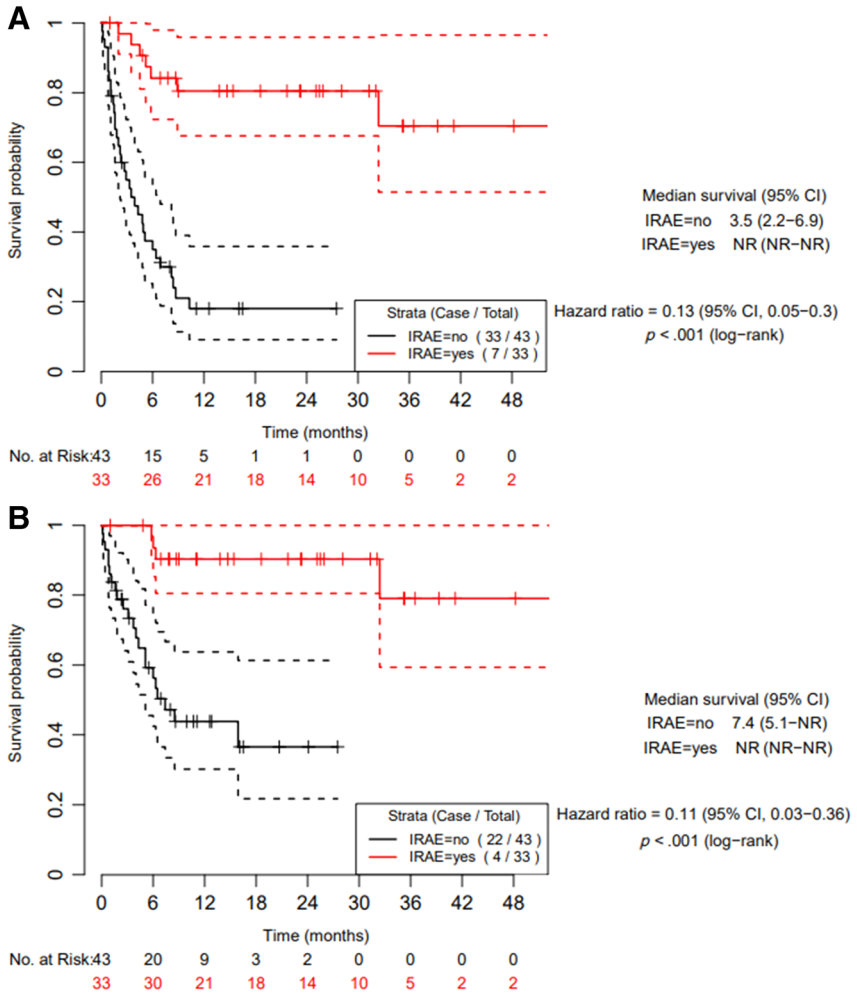

Figure 1. Comparison of progression-free survival and overall survival between study patients who did and did not experience IRAEs. **(A):** Progression-free survival. **(B):** Overall survival.
Abbreviations: CI, confidence interval; IRAE, immune-related adverse event; NR, not reached.

primary tumor type (only in patients with HCC was statistical significance for the secondary OS endpoint not met) and gender. Patients with HCC had the fewest IRAEs (eight) relative to other cohorts, and it is likely because of the lack of events in this cohort (only one death) that OS differences between patients with and without IRAEs did not meet statistical significance. We did not find significant differences in PFS and OS among patients who experienced IRAEs by either initial IRAE severity, management, or TTO. This may largely have been due to sample size limitations given that only 34 patients in our cohort experienced IRAEs.

The percentage (43%) of patients within our cohort who experienced IRAEs is lower than that reported in other GI cancer cohorts (66%–83%) from studies such as Checkmate 142, Checkmate 040, and Keynote 164. This discrepancy can be explained by our choice to record only organ-specific IRAEs, rather than constitutional IRAEs, in our patients [8, 9, 22]. The distribution of IRAEs in our analysis by grade (72% G1/G2, 28% G3/G4) parallels the IRAE distribution from these other cohorts (70%–82% G1/G2). Although the most frequent sites of IRAE involvement in patients from our series (musculoskeletal, dermatologic, and endocrine) were also observed in patients from other series, somewhat surprisingly, no patients in our analysis experienced immune-related diarrhea or colitis. On further investigation, we found that 23% of analyzed patients experienced G1 diarrhea at baseline. Because this did not worsen in any of the patients while they received ICIs, diarrhea did not qualify as an IRAE. The baseline rate of diarrhea in our patient population masked the rates of low-grade immune-related diarrhea experienced by the study population. Colitis is reported to occur in <3% of patients receiving treatment with anti-PD-1 antibodies, and it is possible, based on statistical chance, that none of the patients in the analysis would have experienced this IRAE [23].

Patients with MSI-H tumors were more likely to experience IRAEs than patients with MSI-unknown tumors. All patients with MSI-unknown tumor status had HCC or gastric/GEJ tumors. In HCC, MSI-H status has been reported in <1% of tumors, whereas in gastric/GEJ carcinoma this rate is 10% to 15% [24]. Even if all patients had MSI tumor testing available, based on these baseline rates, the association between MSI-H tumor status and increased IRAEs would have been unchanged. One possible hypothesis for this finding is that MSI-H tumors express a more diverse array of neoantigens than microsatellite stable tumors. It is possible this leads to a

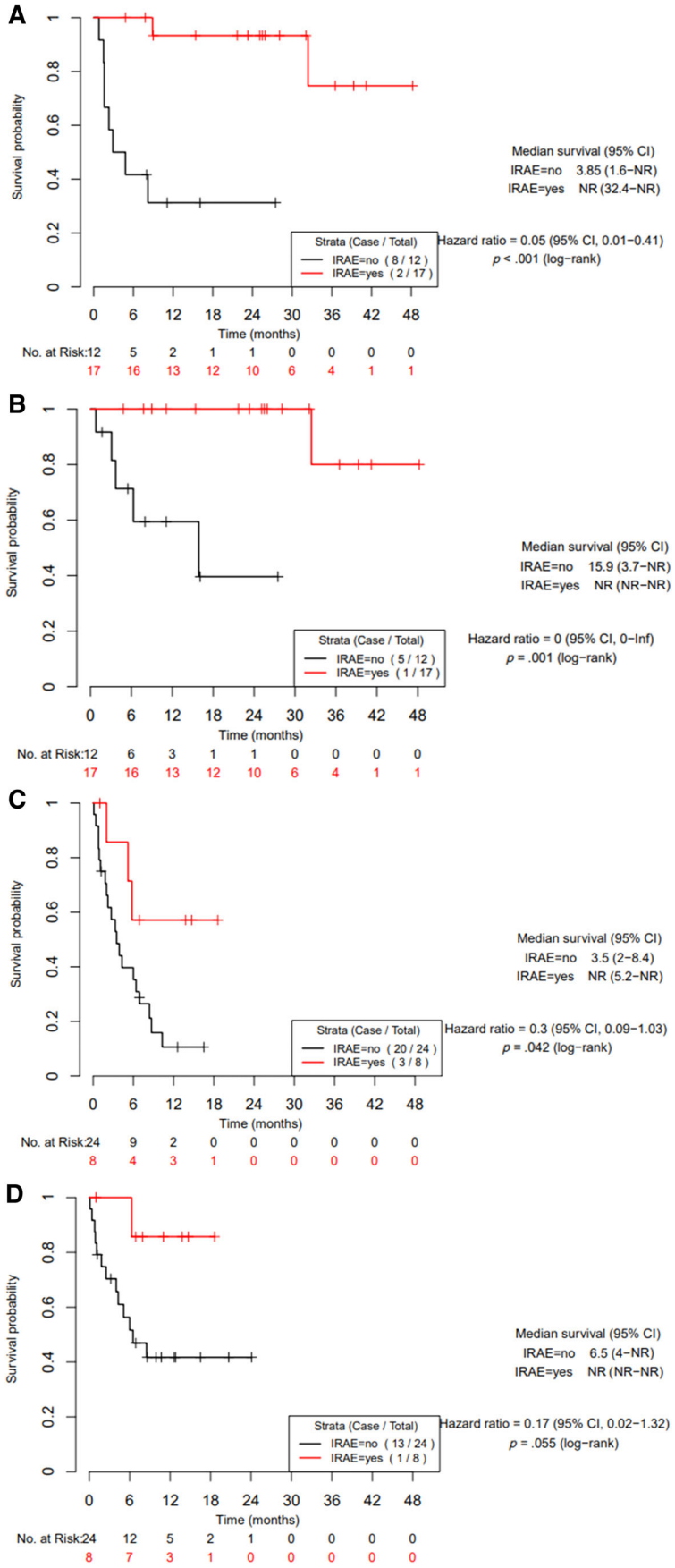

Figure 2. *(Continued on next page).*

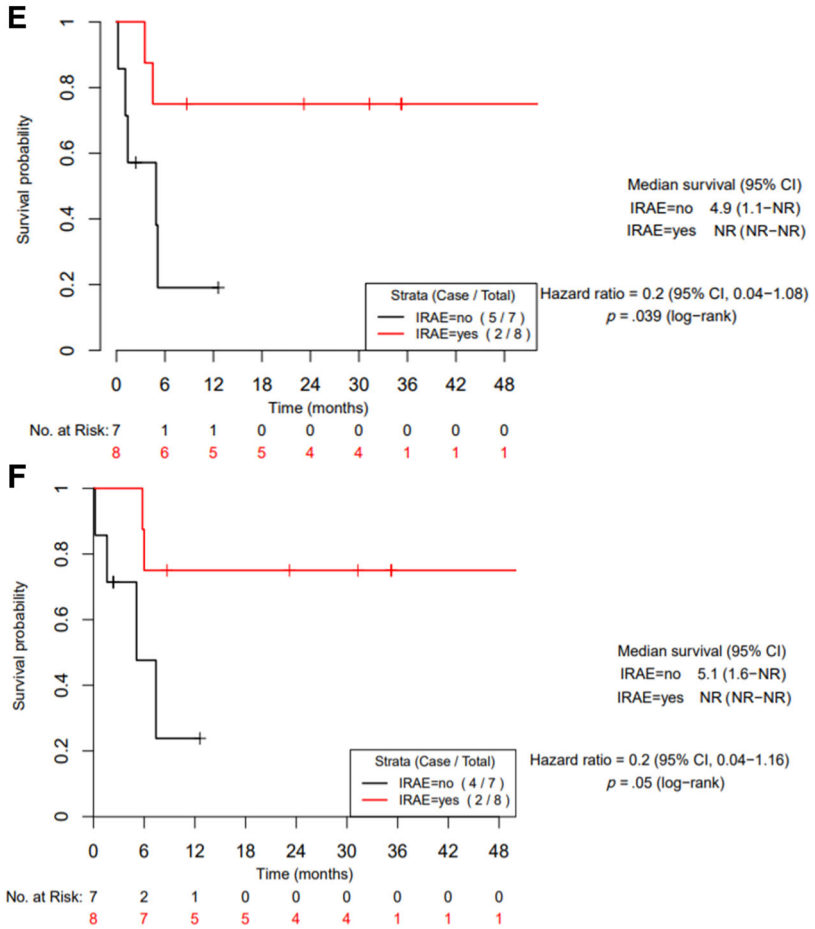

Figure 2. Comparison of progression-free survival (PFS) and overall survival (OS) between study patients who did and did not experience IRAEs by primary tumor type (colorectal, hepatocellular, other). **(A):** PFS of patients with colorectal cancer. **(B):** OS of patients with colorectal cancer. **(C):** PFS of patients with hepatocellular cancer. **(D):** OS of patients with hepatocellular cancer. **(E):** PFS of patients with other tumors. **(F):** OS of patients with other tumors.
Abbreviations: CI, confidence interval; IRAE, immune-related adverse event; NR, not reached.

greater likelihood that some of the antigens presented by MSI-H tumors are present on normal organs [25, 26]. In this instance, ICI treatment would more likely lead to autoimmunity accompanying antitumor activity. To the best of our knowledge, no existing studies have specifically explored mechanisms of autoimmunity in patients with MSI-H tumors receiving ICIs. This may be a research area that warrants future exploration given the potential allure of separating toxicity of ICIs from antitumor activity of the agents. No differences in initial G3/G4 and G1/G2 IRAEs were observed between patients with MSI-H and MSI-unknown tumors.

Several other studies have explored the relationship between IRAEs and ICI efficacy in patients with advanced non-GI malignancies and provide context for our findings. In these other studies, just as in our study, the magnitude of differential benefit between patients who did and did not experience IRAEs while on anti-PD-1 antibody therapy was marked [13–18]. Beyond demonstrating the association between IRAE onset and ICI efficacy, a small number of these studies also examined whether IRAE features (severity, site of involvement, TTO, and management) influence ICI efficacy.

First, looking at IRAE severity, a retrospective analysis of 270 patients with NSCLC treated with anti-PD-1 and anti-PD-L1 antibodies, found no differences in PFS, OS, and RR between patients with G1 IRAEs and those with >G1 IRAEs [18]. In another retrospective analysis of 576 patients with melanoma, patients who experienced G3/G4 IRAEs had no improvement in objective RR compared with those with lower grade IRAEs [27].

Second, looking at IRAE site, endocrine and dermatologic autoimmune toxicities have been associated with ICI efficacy in several studies [28–30]. A recent publication, however, suggests that IRAE sites associated with ICI efficacy may have more to do with shared antigens between tumor and involved site rather than any intrinsic association between ICI and IRAE site [26]. Further investigation is needed to clarify whether certain ICIs have predictive organ-specific IRAEs or whether organ-specific IRAEs result strictly from shared antigens between site and tumor.

Third, looking at IRAE TTO, there is more heterogeneity between studies regarding whether IRAE timing plays a role in ICI response. Some studies suggest that IRAE onset at any time point is associated with improved patient outcomes, whereas others suggest that earlier onset is associated with better patient outcomes [31, 32]. Finally, with regard to steroidal versus nonsteroidal IRAE management, a

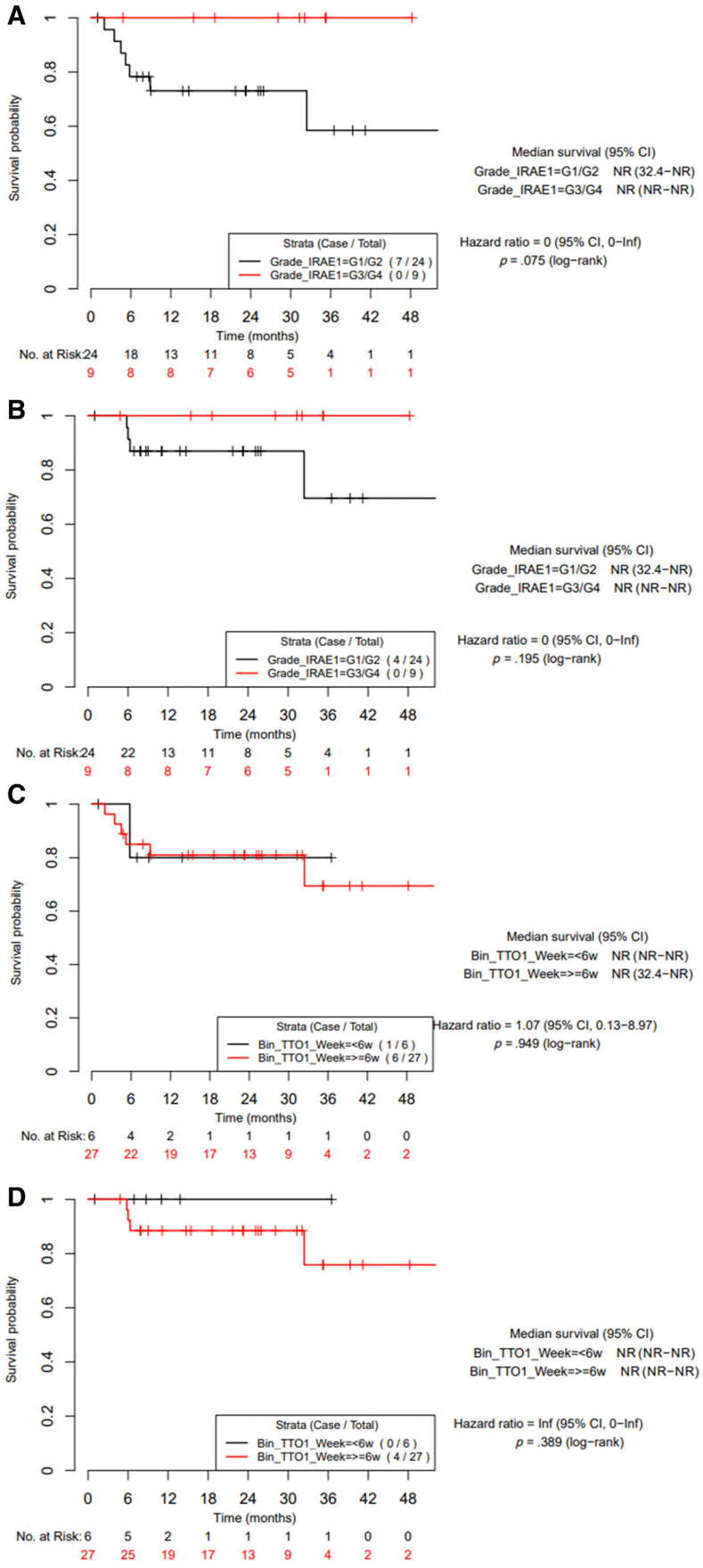

Figure 3. *(Continued on next page)*.

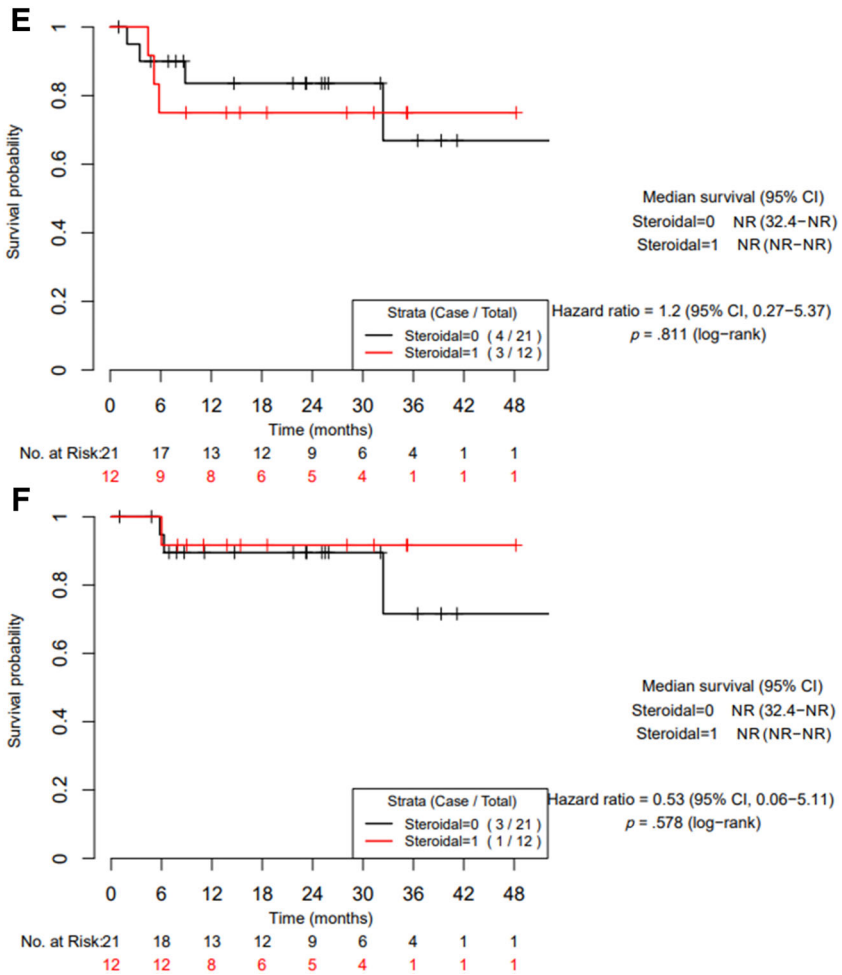

Figure 3. Comparison of progression-free survival (PFS) and overall survival (OS) between study patients who experienced IRAEs by IRAE severity (G3/G4 vs. G1/G2), time to onset (<6 weeks vs. ≥6 weeks), and management (steroidal vs. nonsteroidal). **(A):** PFS of patients by IRAE severity. **(B):** OS of patients by IRAE severity. **(C):** PFS of patients by IRAE time to onset. **(D):** OS of patients by IRAE time to onset. **(E):** PFS of patients by IRAE management. 1 = steroids, 0 = not involving steroids. **(F):** OS of patients by IRAE management. 1 = steroids, 0 = not involving steroids.
Abbreviations: CI, confidence interval; G, grade; IRAE, immune-related adverse event; NR, not reached.; TTO, time to onset.

more uniform consensus exists in published literature about ICI efficacy. Patients who require corticosteroids for IRAE management do not appear to have worse outcomes compared with patients who do not require them [33].

Findings from patients with other tumor types, along with those from our analysis, suggest there may be a universality to the association between IRAE onset and anti-PD-1 antibody response. An initial concern for all studies exploring the association between IRAE onset and anti-PD-1 antibody response was guarantee-time bias, or the notion that patients who experience IRAEs are those who remain on ICIs for longer time periods and thus have a better prognosis than those who do not, by virtue of their disease biology. This has since been proven to be less likely based on results from adjuvant studies demonstrating that the hazard of death or relapse is reduced after IRAE onset compared with before IRAE onset [21]. Still, a multitude of questions pertaining to the nuances of the association between IRAEs and ICI efficacy exist. Specifically, how IRAE severity, site, TTO, and management affect ICI response remain largely undefined. Furthermore, the associations between tissue biomarkers of ICI response (MSI-H, TMB, PD-L1) and IRAEs are even less well understood biologically. Once these nuances are better understood, IRAE onset could become the first clinical biomarker for anti-PD-1 antibody response in patients with indications to receive ICIs and guide oncologists facing the dilemma of whether to continue an ICI in a patient with equivocal imaging findings or mixed clinical response.

Limitations

Our analysis, and the overall potential for IRAEs as a biomarker for ICI response, carry some inherent limitations. First, focusing on our analysis, it was retrospective. As such, possible bias could have been introduced during the process of data collection. Interobserver variability between investigators at each site during chart review could have led to differences in IRAE grading, although CTCAE version 5.0 was utilized in all instances. Interinstitutional variability between radiologists could have led to different interpretations of RECIST 1.1 criteria when determining response. The potential bias in the data collection process is inherent to any multi-

institution research effort; however, it is less likely in prospective trials where central imaging review and rigorous data evaluation occurs regularly. We also had a limited sample size given the rarity of patients with GI cancer with FDA-approved indications to receive ICIs. This minimized our ability to identify specific IRAE characteristics that were associated with ICI response. We were also limited in our ability to correlate tissue biomarkers with IRAE occurrence; we were only able to correlate MSI-H tumor status with IRAEs and were unable to so with TMB given the small number of patients who had this information available. A significant proportion of our patients (46%) possessed MSI-H tumors, raising the question of whether our findings are generalizable to the other GI tumor types included in the analysis. The consistent results we observed between IRAE onset and ICI efficacy in the HCC and other tumor cohorts (composed predominantly of GA/GEJ tumors) make this concern less likely.

Next, looking to the limitations of IRAE onset as a biomarker for ICI response, IRAEs only occur after patients start therapy and therefore cannot be used to determine which patients should receive ICIs. Furthermore, patients who do not experience IRAEs while on ICIs can still derive benefit from the treatment. It is also unclear, from our analysis and existing literature, whether more severe IRAEs or greater number of IRAEs represent a surrogate for more robust antitumor activity and potentially increased ICI responsiveness. For now, the only possible utility of IRAE onset is to provide a supporting piece of information to a treating oncologist who is continuing a patient on an ICI in the setting of equivocal imaging findings or unclear clinical response.

Conclusion

Emerging evidence across tumor types suggests that patients who experience IRAEs while on therapy with anti-PD-1 antibodies have improved outcomes. To the best of our knowledge, this analysis is the first to report this phenomenon in a multidisease cohort of patients with GI cancer treated with anti-PD-1 antibodies for FDA-approved indications. Specifically, we found significant differences in PFS and OS between patients with GI cancer on anti-PD-1 antibodies based on IRAE presence. Among patients who experienced IRAEs, we did not find statistically significant associations between ICI efficacy and either initial IRAE severity, management, or TTO, perhaps because of limited sample size. In patients with advanced cancer receiving anti-PD-1 antibodies, the nuances of the relationship between IRAE onset and ICI efficacy remain largely undefined and will require more rigorous prospective evaluation before IRAE onset can be clinically adopted as an on-treatment biomarker for anti-PD-1 antibody response. Beyond the role of IRAEs as a biomarker, studying them may provide insights into the biological mechanisms that govern the relationship between autoimmunity and antitumor activity of checkpoint inhibitors. This may one day lead to the uncoupling of autoimmunity from antitumor activity in patients with advanced cancer receiving ICIs, which would be of tremendous value to the field.

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Disclosures

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